Published in final edited form as:

Am J Surg Pathol. 2019 April ; 43(4): 559–563. doi:10.1097/PAS.0000000000001225.

Impact of peritoneal metastasis on survival of patients with small intestinal neuroendocrine tumor

M. Frances Wright, MD¹, Justin Cates, MD, PhD¹, Raul S. Gonzales, MD², Satya Das, MD³, Jordan D. Berlin, MD³, and Chanjuan Shi, MD, PhD¹

¹Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN

²Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA

³Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Abstract

The liver and peritoneum are the two most common distant metastatic sites for small intestinal neuroendocrine tumors (SI-NET). In this study, we evaluated the differential impact of hepatic and/or peritoneal metastasis on prognosis of SI-NET patients. Surgical Pathology archives were searched for SI-NET resections performed between 01/01/1994 and 08/31/2017. Two hundred and nineteen cases with clinical follow-up data were identified. Pathology reports and electronic medical records were reviewed. The 219 patients included 104 females and 115 males with a median age of 59 years (range, 19-85). There were 71 (33%) cases without hepatic or peritoneal metastasis, 80 (37%) with hepatic metastasis only, 14 (6%) with peritoneal metastasis only, and 53 (24%) with both hepatic and peritoneal metastasis at the time of surgery or during follow-up. The number of primary tumors, largest tumor size, lymph node metastasis, pT category, and sex were not significant independent prognostic factors in multivariate Cox proportional hazard regression. Age was the only variable other than presence of metastatic disease that was associated with worse prognosis (5% increase in risk/year of age; 95% CI 1.7-8.2%; $P=0.003$). After controlling for patient age, pairwise comparisons of marginal linear predictions showed increased risk with peritoneal metastasis, with or without associated hepatic metastasis, compared to hepatic metastasis only. In conclusion, although limited by the number of patients with peritoneal metastasis only, these results support sub-stratifying patients with metastatic SI-NET by anatomic site of metastasis.

Keywords

small intestinal neuroendocrine tumor; liver metastasis; peritoneal metastasis; prognosis

INTRODUCTION

Small intestinal neuroendocrine tumors (SI-NETs) are the most common small bowel malignancy in the United States, and incidence is increasing [1,2,3]. Diagnosis is often delayed due to the typically small size, slow growth rate, submucosal location, and asymptomatic nature of these tumors [4,5]. By the time of diagnosis, 25-50% of patients already have distant metastases (Stage IV disease) [6,7,8].

Historically, accurate staging of SI-NETs has been problematic due to low prevalence and characteristically indolent disease course [1]. Multiple studies have shown overlap in survival rates among American Joint Committee on Cancer (AJCC) 7th edition Stages I-III disease [1,2,9,10]. The 5- and 10-year survival for Stage IV disease, however, is consistently and significantly worse [6,7,9,10]. Nevertheless, Stage IV SI-NETs exhibit heterogeneous clinical behavior; survival for patients with hepatic metastases spans from under two to over ten years [11,12]. Panzuto et al previously reported that metastatic pattern affected progression free survival in a cohort of patients with Stage IV pancreatic or small intestinal NETs, but their analysis was restricted to unilobar and bilobar liver metastases and extra-abdominal metastases [13]. The variability of outcomes of Stage IV disease highlights the need for improved prognostic stratification in this group.

The recently published 8th edition of the AJCC Cancer Staging Manual subclassifies M staging by site of metastatic disease: M1a (hepatic only), M1b (extrahepatic only), and M1c (hepatic and extrahepatic) [14]. The prognostic significance of these categories is not yet established. The peritoneum is reportedly the third most common site of metastasis after the liver and lymph nodes [15]; therefore, it serves as a useful representative of distant extrahepatic metastatic disease. In this study, we analyzed 219 patients with resected midgut NET(s) and were able to clarify the prognostic significance of peritoneal metastasis in these patients, both isolated and in the setting of hepatic metastasis, thus supporting the current AJCC M stage subclassification.

MATERIALS AND METHODS

The surgical pathology archives at Vanderbilt University Medical Center were searched for midgut small intestinal (jejunal/ileal) neuroendocrine tumors resected between 01/01/1991 and 08/31/2017. Cases were excluded if the resection specimen was not reviewed at VUMC or if clinical follow-up data were unavailable. A total of 219 cases met inclusion criteria. Electronic medical records were reviewed for demographic data, date of surgery, operative notes, follow-up data, treatment history, and duration of follow-up. The presence or absence of peritoneal and/or liver metastases was adjudicated based on pathology reports, radiologic studies, and operative notes. Peritoneal metastasis ranged from scattered small tumor nodules on the peritoneal surface identified during surgery and gross pathological examination (Figure 1A), radiographic documentation of peritoneal nodules, to peritoneal carcinomatosis with omental caking (Figure 1B). Primary tumor size and number, AJCC pT category, presence or absence of lymph node metastasis, and WHO grade (based on immunohistochemical Ki67 index) were recorded from surgical pathology reports. In addition, the Ki67 index in 106 was abstracted from previous studies [16]. This retrospective

study was approved by the Institutional Review Board at Vanderbilt University Medical Center.

Analyses of associations between site of metastasis (hepatic or peritoneal metastasis) and other clinicopathologic variables were performed using standard bivariate methods. Factors associated with disease-specific survival (DSS) were assessed by univariate Cox proportional hazard regression. Since only age and presence of metastatic disease were significant cofactors in univariate regression, subsequent regression models of site of metastasis were adjusted for patient age. Statistical analyses were performed using Stata 13 (Stata Corp, College Station, TX). All hypothesis tests were two-sided with $\alpha=0.05$.

RESULTS

Demographics and clinicopathologic features

Demographic and clinicopathologic data stratified by site of distant metastasis are summarized in Table 1. Median age was 59 years (range 19 to 85 years). Mean primary lesion size was 2.0 cm (0.9-8.0 cm). Median follow-up was 61 months (range 0.3-313 months). Seventy-one (33%) patients had neither hepatic nor peritoneal metastases at any point during clinical follow-up, 80 (37%) had only hepatic metastasis, 14 (6%) had only peritoneal metastasis, and 53 (24%) had both hepatic and peritoneal metastasis. Distant metastases developed during clinical follow-up in 13 cases, including 11 with only hepatic metastasis, and 2 with both hepatic and peritoneal metastasis. In 4 of these cases, computed tomography was used for pre-operative clinical staging and metastatic disease was discovered by high resolution magnetic resonance imaging studies performed within 3-6 months of surgical resection of the primary tumor. At last follow-up, 48 patients (22%) were alive without evidence of disease, 107 (49%) were alive with persistent disease, 51 (23%) had died of disease, and 13 (6%) had died of other causes.

Peritoneal metastasis, but not hepatic metastasis alone, is associated with shorter disease-specific survival

Univariate and multivariate statistical analyses were performed to determine predictors of shorter disease-specific survival (DSS). In univariate analyses, increasing age and presence of peritoneal metastasis (with or without concomitant hepatic metastasis), were the only clinicopathologic variables significantly associated with shorter DSS (Table 2). Other factors, including male sex, primary tumor size, number of primary tumors, WHO grade, AJCC pT category, and lymph node metastasis, were not significantly associated with shorter DSS. Subsequent survival analysis adjusting for patient age confirmed that patients with peritoneal metastasis, with or without associated hepatic metastasis, showed significantly shorter DSS (Table 2). Hepatic metastasis alone showed a trend towards decreased DSS, but this association did not achieve statistical significance. Hazard ratios associated with peritoneal metastasis only (9.85; 95% CI 1.91-50.86, $P<0.05$) and combined hepatic and peritoneal metastases (8.66; 95% CI 2.05-36.58, $P<0.005$) were similar; both were significantly greater than that for hepatic metastasis alone (3.40; 95% CI 0.77-14.99, $P=0.11$) (Table 3). Kaplan-Meier survival curves by anatomic site of metastasis are plotted in Figure 2.

Median survival for patients with liver metastasis only was 156 months, compared to 133 months for patients with peritoneal metastasis and 82 months for patients with combined hepatic/peritoneal metastasis. Median survival for patients without metastasis was not reached during follow-up.

One hundred and two patients (47%) received additional treatment(s) following surgery, including octreotide (n=98), everolimus (n=11), capecitabine (n=6), and/or peptide receptor radionuclide therapy (PRRT) (n=4). No patients in this series received hyperthermic intraperitoneal chemotherapy. These patients who received additional treatment(s) had significantly shorter DSS (hazard ratio 2.59; 95% CI 1.25-5.26; P=0.01; Table 2), reflecting our institutional practice of only administering these therapies to patients with high volume of metastatic disease and/or rapid progression.

Peritoneal metastasis is associated with advanced T category

Comparing clinicopathologic variables by the presence or absence of peritoneal metastasis revealed that higher T category was associated with hepatic and peritoneal metastases or peritoneal metastasis only (Table 1). The presence of lymph node metastasis was also associated with peritoneal or combined sites of metastasis. There was no statistically significant association between site of metastasis and patient sex, higher WHO grade, or the presence of multiple primary lesions.

DISCUSSION

Peritoneal involvement in SI-NET is common (reported frequency of 10-33%) and has a range of gross pathologic presentations, from small isolated nodules to carcinomatosis [15,17,18]. In the cohort reported here, 67 of 219 patients (31%) had peritoneal metastasis either at the time of surgery or during follow-up. All of the retrospective series, like ours, come from tertiary referral sources and it is unknown how our data may differ from the general population of SI-NET patients.

There is relatively little literature regarding peritoneal disease in SI-NET. In this study, we reported that approximately a third of patients with SI-NET had peritoneal involvement. Peritoneal metastasis was once thought to have no prognostic importance. Perhaps this is because hepatic metastasis is more common, and subsequent liver failure was previously considered to be a major cause of mortality in these patients [17]. Recent studies have reported the poor prognostic implications of peritoneal carcinomatosis/metastasis in the setting of SI-NET and its associated morbidity in the form of intestinal and/or ureteral obstruction [19]. Additionally, a small series study showed that in patients undergoing resection of liver metastases, the presence of extrahepatic metastasis (most frequently peritoneal metastasis) portended worse DSS after liver debulking surgery [11]. Our study has confirmed that peritoneal metastasis is a poor prognosticator in patients with SI-NETs. In addition, patients with peritoneal involvement with or without liver metastases did worse than those with liver metastases only, supporting stratification of M category for patients with stage IV SI-NET.

Compared to liver metastasis, for which there are multiple therapeutic options (surgical resection, liver transplantation, transcatheter embolization, radiofrequency ablation, and cryotherapy) [20], there are no widely available treatments for peritoneal disease besides somatostatin analogues, chemotherapy and now PRRT [17]. Research in this area has been limited. Elias et al reported on outcomes of patients with peritoneal carcinomatosis who underwent peritonectomy with or without hyperthermic intraperitoneal chemotherapy (HIPEC). While their data suggested a survival benefit among those undergoing peritonectomy, there was no control group for comparison. Moreover, HIPEC was abandoned partway through the study due to associated morbidity, uncertainty regarding its benefit in the setting of a relatively indolent tumor, and preliminary data showing no overall survival benefit [17]. The aforementioned treatments for liver metastasis, on the other hand, improve symptoms and increase overall survival rates [20, 21].

Our data also showed that the presence of either peritoneal metastasis only or combined hepatic and peritoneal metastasis was significantly associated with higher pT category. This is consistent with the understanding that one of the etiologies of peritoneal metastasis is exfoliation of tumor cells from a primary tumor or metastatic focus that has invaded through anatomical structures to involve the serosal surface [22].

In summary, our data support previous studies citing peritoneal involvement as a poor prognostic factor in SI-NET, and this is the first study specifically evaluating its effect relative to isolated or concomitant hepatic metastasis. Our data show that peritoneal metastasis, both with or without associated hepatic metastasis, portends worse DSS than hepatic metastasis alone, and that the presence of peritoneal metastasis, with or without hepatic metastasis, is associated with higher T category. These findings support the new 8th edition AJCC sub-stratification of metastatic disease. However, ultimate validation of this system will require prospective data collection and the inclusion of all sites of extrahepatic metastasis.

ACKNOWLEDGEMENT:

This study is supported by NIH/NIDDK 5P30 DK058404-13 (CS) and NIH/NCI 5P50 CA095103-13 (CS).

REFERENCES

1. Sun Y, Lohse C, Smyrk T, et al. The influence of tumor stage on the prognostic value of Ki-67 and mitotic count in small intestinal neuroendocrine tumors. *Am J Surg Pathol*. 2018;42:247–255. [PubMed: 29016403]
2. Kim MK, Warner RR, Roayaie S, et al. Revised staging classification improves outcome prediction for small intestinal neuroendocrine tumors. *J Clin Oncol*. 2013;31:3776–3781. [PubMed: 24043726]
3. Wu L, Fu J, Wan L, et al. Survival outcomes and surgical intervention of small intestinal neuroendocrine tumors: a population based retrospective study. *Oncotarget*. 2017;8:4935–4947. [PubMed: 27903960]
4. Mantzoros I, Savvala NA, Ioannidis O, et al. Midgut neuroendocrine tumor presenting with acute intestinal ischemia. *World J Gastroenterol*. 2017;23:8090–8096. [PubMed: 29259385]
5. Modlin IM, Kidd M, Latich I, et al. Current status of gastrointestinal carcinoids. *Gastroenterology*. 2005;128:1717–1751. [PubMed: 15887161]
6. Landerholm K, Zar N, Andersson RE, et al. Survival and prognostic factors in patients with small bowel carcinoid tumour. *Br J Surg*. 2011;98:1617–1624. [PubMed: 21858790]

7. Modlin IM, Champaneria MC, Chan AK, et al. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. *Am J Gastroenterology*. 2007;102:1464–1473.
8. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer*. 2009;16:885–894. [PubMed: 19458024]
9. Strosberg JR, Weber JM, Feldman M, et al. Prognostic validity of the American Joint Committee on Cancer staging classification for midgut neuroendocrine tumors. *J Clin Oncol*. 2013;31:420–425. [PubMed: 23248248]
10. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer*. 2011;117:3332–3341. [PubMed: 21246527]
11. Bertani E, Falconi M, Grana C, et al. Small intestinal neuroendocrine tumors with liver metastases and resection of the primary: Prognostic factors for decision making. *Int J Surg*. 2015;20:58–64. [PubMed: 26074290]
12. Shi C, Gonzalez RS, Zhao Z, et al. Liver Metastases of Small Intestine Neuroendocrine Tumors: Ki67 heterogeneity and WHO grade discordance with primary tumors. *Am J Clin Pathol*. 2015;143:398–404. [PubMed: 25696798]
13. Panzuto F, Merola E, Rinzivillo M, et al. Advanced digestive neuroendocrine tumors: metastatic pattern is an independent factor affecting outcome. *Pancreas*. 2014;43:212–218. [PubMed: 24518498]
14. Woltering EA, Bergsland E, Beyer DT, Amin MB. Neuroendocrine tumors of the jejunum and ileum *AJCC Cancer Staging Manual*, 8th ed. Chicago, IL: Springer; 2017:375–387.
15. Norlen O, Edfeldt K, Akerstrom G, et al. Peritoneal carcinomatosis from small intestinal neuroendocrine tumors: Clinical course and genetic profiling. *Surgery*. 2014;156:1512–1521; discussion 1521-1522. [PubMed: 25456945]
16. Fata CR, Gonzalez RS, Liu E, et al. Mesenteric tumor deposits in midgut small intestinal neuroendocrine tumors are a stronger indicator than lymph node metastasis for liver metastasis and poor prognosis. *Am J Surg Pathol*. 2017;41:128–133. [PubMed: 27684993]
17. Elias D, David A, Sourrouille I, et al. Neuroendocrine carcinomas: optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). *Surgery*. 2014;155:5–12. [PubMed: 24084595]
18. Kianmanesh R, Ruzsniowski P, Rindi G, et al. ENETS consensus guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors. *Neuroendocrinology*. 2010;91:333–40. [PubMed: 20424420]
19. Norlen O, Stalberg P, Oberg K, et al. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg*. 2012;36:1419–1431. [PubMed: 21984144]
20. Saeed A, Buell JF, Kandil E. Surgical treatment of liver metastases in patients with neuroendocrine tumors. *Ann Transl Med*. 2013;1:6. [PubMed: 25332951]
21. Kennedy A, Bester L, Salem R, et al. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumors (NET): guidelines from the NET-Liver-Metastases Consensus Conference. *HPB (Oxford)*. 2015;17:29–37. [PubMed: 25186181]
22. Hase K, Ueno H, Kuranaga N, et al. Intraperitoneal exfoliated cancer cells in patients with colorectal cancer. *Dis Colon Rectum*. 1998;41:1134–1140. [PubMed: 9749497]

Figure 1:
Peritoneal involvement by small intestinal neuroendocrine tumor (NET). A. Peritoneal nodule (original magnification 20X); B. A representative section from NET omental cake (original magnification 20X).

Figure 2:
Cox proportional hazard regression according to metastatic site (adjusted for patient age).

TABLE 1.

Overall Patient Demographics and Clinicopathologic Features Stratified By Site of Distant Metastasis (Total N=219)

	N	None	Liver only	Peritoneal only	Liver and peritoneal	P
Sex	218					0.664
Female		30 (42%)	41 (51%)	6 (43%)	27 (51%)	
Male		41 (58%)	39 (49%)	8 (57%)	26 (49%)	
T category	214					0.0005
1		5 (7%)	2 (3%)	0 (0%)	0 (0%)	
2		12 (17%)	7 (9%)	1 (7%)	2 (4%)	
3		36 (51%)	50 (64%)	6 (43%)	26 (51%)	
4		18 (25%)	19 (24%)	7 (50%)	23 (45%)	
Primary lesion #	214					0.468
Single		48 (68%)	51 (65%)	6 (46%)	36 (69%)	
Multiple		23 (32%)	27 (35%)	7 (54%)	16 (31%)	
WHO grade	171					0.075
1		52 (84%)	40 (67%)	7 (78%)	27 (68%)	
2		10 (16%)	20 (33%)	2 (22%)	11 (27%)	
3		0 (0%)	0 (0%)	0 (0%)	2 (5%)	
LN metastasis	204					0.004
Absent		18 (26%)	5 (7%)	0 (0%)	6 (12%)	
Present		50 (74%)	69 (93%)	13 (100%)	43 (88%)	

TABLE 2.

Potential Predictors of Disease-Specific Survival in Patients with SI-NET

	Univariate Analysis			Multivariate (age-centered) Analysis		
	HR	95% CI	P	HR	95% CI	P
Male sex	1.02	0.58-1.78	0.94			
Age (years)	1.05	1.02-1.08	0.001			
Tumor size (cm)	1.04	0.82-1.33	0.72			
Multiple lesions	0.94	0.52-1.69	0.84			
WHO grade						
Grade 2-3	1.69	0.81-3.51	0.16			
T category						
pT3	1.84	0.64-5.27	0.25			
pT4	2.00	0.67-5.99	0.22			
LN metastasis	1.02	0.40-2.60	0.96			
Liver/peritoneal met						
Liver only	3.34	0.76-14.66	0.11	3.40	0.77-14.99	0.11
Peritoneal only	9.28	1.80-47.93	0.008	9.85	1.91-50.86	0.006
Liver and Peritoneal	9.26	2.19-39.06	0.002	8.66	2.05-36.58	0.003
Additional treatment	2.59	1.25-5.26	0.01			

Abbreviations: HR, hazard ratio; met, metastasis.

Note: age and tumor size were entered as continuous variables; WHO Grade 2 and 3 tumors were compared with WHO Grade 1 tumors; pT3 and pT4 tumors were compared to pT1 and pT2 tumors combined; the presence of liver and/or peritoneal metastases was compared to absence of distant metastasis.

TABLE 3.

Cox proportional hazard regression according to metastatic profile

	HR	95% CI	P
Liver only vs none	3.40	0.77-14.99	0.11
Peritoneal only vs none	9.85	1.91-50.86	0.006
Liver + peritoneal vs none	8.66	2.05-36.58	0.003
Peritoneal only vs liver only	2.90	1.04-8.08	0.042
Liver + peritoneal vs liver only	2.55	1.35-4.79	0.004
Liver + peritoneal vs peritoneal only	0.88	0.34-2.31	0.79

None = no distant metastasis